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Fundamental Study of Positive Contrast Media of Hepatic CT by Micro-Barium Sulphate Particles

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Key Words : Micro-barium sulphate particles, Contrast medium, CT, Liver

微細バリウム粒子を用いた肝CTにおける陽性造影剤の基礎的研究

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肝CTにおける陽性造影剤の基礎的研究として，粒子の経静脈投与によって起こる肝のCT値の変化及び組織学的変化を比較検討した．

実験に用いた粒子は0.3μ及び1.2μの大きさの硫酸バリウム粒子10%溶液で，2ml/kgの投与量でラットに経静脈投与を行った．投与直後の平均の肝CT値は投与前のCT値と比べて0.3μ粒子で2.3倍，1.2μ粒子で2.7倍の増加を示した．その後CT値は，時間の経過と共に減少し，投与後30日で投与直後のCT値の1/2に，120日では1/5の値となった．

同時期に行ったラット肝の組織学的検索により，肝CTの造影効果は主にperiportal regionにおけるKupffer細胞による粒子の貪食により与えられ，その後各Kupffer細胞に貪食された粒子の量の減少と，粒子を貪食したKupffer細胞の数の減少によりCT値は低下するものと考えられた．

Introduction

The administration of a contrast medium is essential for improvement of lesion enhancement in computed tomography (CT) of the liver. It is especially important in hepatocellular carcinoma and metastatic hepatic tumor since their prognoses depend mostly on the early and accurate detection of daughter cells or small lesions[1)2)]. Water-soluble contrast media are generally used for this purpose. These, however, are not ideal since they may fail to demonstrate small lesions due to the need to increase the dose to enhance effectively a whole area of the liver for a sufficiently long period of time[1)3)~7)]. In addition, small tumors cannot be sharply demarcated from adjoining normal tissues, since water-soluble contrast media get not only into normal tissues but also into extracellular spaces of tumors[3)~5)8)9)].

Accordingly, various materials have been studied as positive contrast media of the liver on an experimental basis[1)3)~32)] (Table 1) and some of them have already come into clinical use[1)9)14)~16)26)]. They

Table 1 List of hepatic contrast medium.

Name of contrast medium	Reference
Thorotrast	Dickson W.H. 1932 (30)
Barium sulphate	Teplick J.G. 1957 (10)
Colloidal tin (stannic) oxide	Fischer H.W. 1957 (27)
Tetraiodophenolphthalein	Zimmon D.S. 1965 (22)
AG52-315, AG 60-99	Vermess M. 1974 (25) Laval-Jeantet M. 1976 (26)
Iothalamate ethyl ester	Fischer H.W. 1977 (29)
Heavy metal particles AgI, CeO_2, Gd_2O_3, Dy_2O_3	Seltzer S.E. 1979 (28)
Ethiodized oil emulsion13(EOE-13)	Vermess M. 1979 (17)
Iodipamide ethyl ester	Violante M.R. 1980 (7)
Iodinated starch particles	Cohen Z. 1981 (4)
Liposomes	Havron A. 1981 (24)
Cholesteryl iopanoate	Longino M.A. 1983 (6)

facilitate the detection of small hepatic lesions by the following mechanism. When the various micro-particles are administered intravenously or intraarterially, the hepatic reticuloendothelial system (RES) phagocytizes.them so that the liver is enhanced selectively.

Micro-barium sulphate particles (B.S.P.) are also one of them. The purpose of this study has been to determine when and how much B.S.P. are taken up in the liver and when and how B.S.P. are eliminated from the liver as a fundamental study of positive contrast media. Therefore, we carried out experiments on rats to pursue time-CT values curve of the liver and observe microscopical features of the liver at various time after B.S.P. administration.

Materials and Methods

Male Wister-strain rats weighing 400 g were used as the experimental animals.

100% 0.3 μ and 1.2 μ B.S.P. suspensions (Sakai Chemical CO. Osaka) were diluted to 10% with 5% glucose solution. Immediately after a bottle of B.S.P. suspension had been shaken up by hand, the particles were observed by electron microscopy and injected intravenously.

Ten rats were anesthetized with an intraperitoneal injection of sodium pentobarbiturate at a dose of 0.5 ml/kg. The animals were then secured between beans bags in a prone position on a fixation table made of styrene foam. The liver was scanned by CT to obtain preinjection CT values before the B.S.P. administration. A 0.3 μ or 1.2 μ B.S.P. suspension was then injected intravenously into the tail vein of 10 rats at a dose of 2 ml/kg followed by liver scanning by CT immediately after (at 20 minutes) and at 5, 15, 30, 45, 60, 90 and 120 days after the B.S.P. administration. A 0.3 μ or 1.2 μ B.S.P. suspension was also injected intravenously to additional 2 rats to scan the liver at one year postinjection. Scan was performed downward from the dome of diaphragm with 2 or 3 slices in a slice thickness of 10 mm and a scanning time of 9 sec. The hepatic CT values (H.U.) were obtained on ROI setting as large as possible on the hepatic image. The average CT values were the arithmetic mean of the values from 4 different hepatic sites. The CT machine was a TCT-60A-27CT scanner of Tokyo Shibaura Electric CO. Ltd..

Thirty two rats were anesthetized with an intraperitoneal injection of sodium pentobarbiturate at a dose of 0.5 ml/kg.A 0.3 μ B.S.P. suspension was injected intravenously into the tail vein of one half these animals and a 1.2 μ B.S.P. suspension into the other half, the dose in all cases being 2 ml/kg. Eight rats, 4 from the each suspension group, were sacrificed at the same time immediately after (at 20 minutes) and at 5, 45 and 120 days after the B.S.P. administration. Two other rats were also sacrificed at one year after the B.S.P. administration. The livers were isolated, fixed in formalin, stained with hematoxylin and eosin and observed by light microscopy. The distribution of Kupffer cells containing B.S.P. was observed at a

magnification of 200 times. The region close to Glisson's sheath and that close to the central vein were designated as the periportal and the perivenous region, respectively. Kupffer cells containing B.S.P. in these regions were counted to evaluate the space and time related distribution of the cells immediately after and at 5, 45 and 120 days and one year after B.S.P. administration.

Observation was made at a magnification of 400 times to evaluate the quantity of B.S.P. within the Kupffer cells. The quantity of B.S.P. in the periportal region was classified into three grades, "large", "medium" and "small". The number of Kupffer cells for each grade was counted immediately after and at 5, 45 and 120 days and one year after B.S.P. administration. The results were expressed as percentage.

A 0.3 μ B.S.P. suspension was injected intravenously into one rat at a dose of 2 ml/kg and B.S.P. within Kupffer cells were observed by electron microscopy at 5 days after the B.S.P. administration. The rat was anesthetized with an intraperitoneal injection of sodium pentobarbiturate and prefixed by perfusing its entire body with 2.5% glutaraldehyde from the left ventricle. The liver was then isolated, cut into pieces about 1 mm^3 in size and transferred to 2.5% glutaraldehyde. After fixation at 4°C for 2 hours, the pieces were postfixed in 1% OsO_4 at 4°C for 2 hours, dehydrated through ethanol series and embedded in Epon 812. Semithin sections of the embedded specimen were prepared for stainning with toluidine blue. After the specimen was confirmed to be from the periportal region by light microscopy, ultrathin sections were made and stained finally with uranyl acetate and lead citrate.

Results

1. Size of B.S.P.

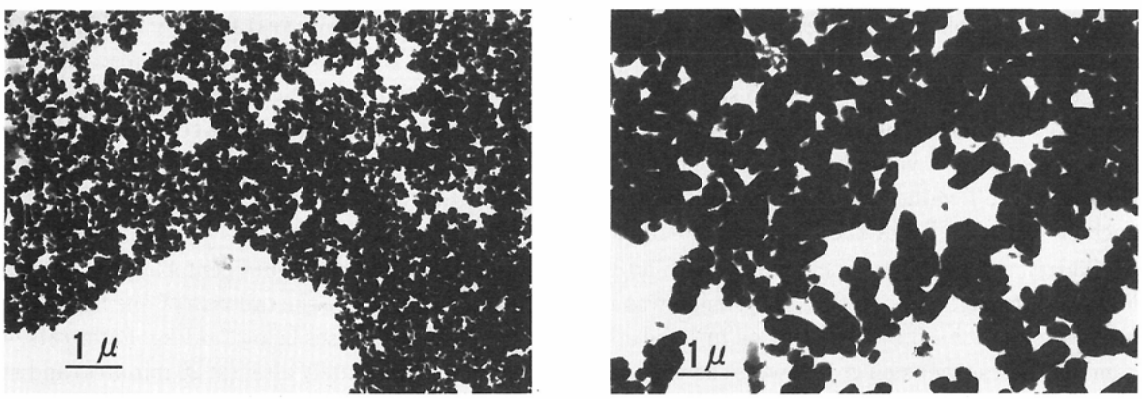
Before the intravenous injection of B.S.P. to rats, the size of B.S.P. was confirmed by electron microscopy, however, the size distribution of B.S.P. was not pursued (Fig. 1a, b).

2. Change of hepatic CT values after B.S.P. administration

The hepatic CT values immediately after the B.S.P. administration were 2.3 and 2.7 times greater in average than the preinjection CT values for the 0.3 μ and 1.2 μ suspension, respectively. After the hepatic CT values reached a maximum, they decreased to one-half at 30 days after and to one-fifth at 120 days after (Fig. 2a, b, c, d and Fig. 3a, b). They decreased to the preinjection CT values one year later.

3. Microscopic study on the number of Kupffer cells containing B.S.P. in the periportal and perivenous regions

When the hepatic CT values showed a maximum, there was an apparent difference in the number of



a b

Fig. 1 Electron micrographs of 10% 0.3 μ (a) and 1.2 μ (b) B.S.P. suspensions. Particles are approximately 0.3 μ or 1.2 μ in diameter.

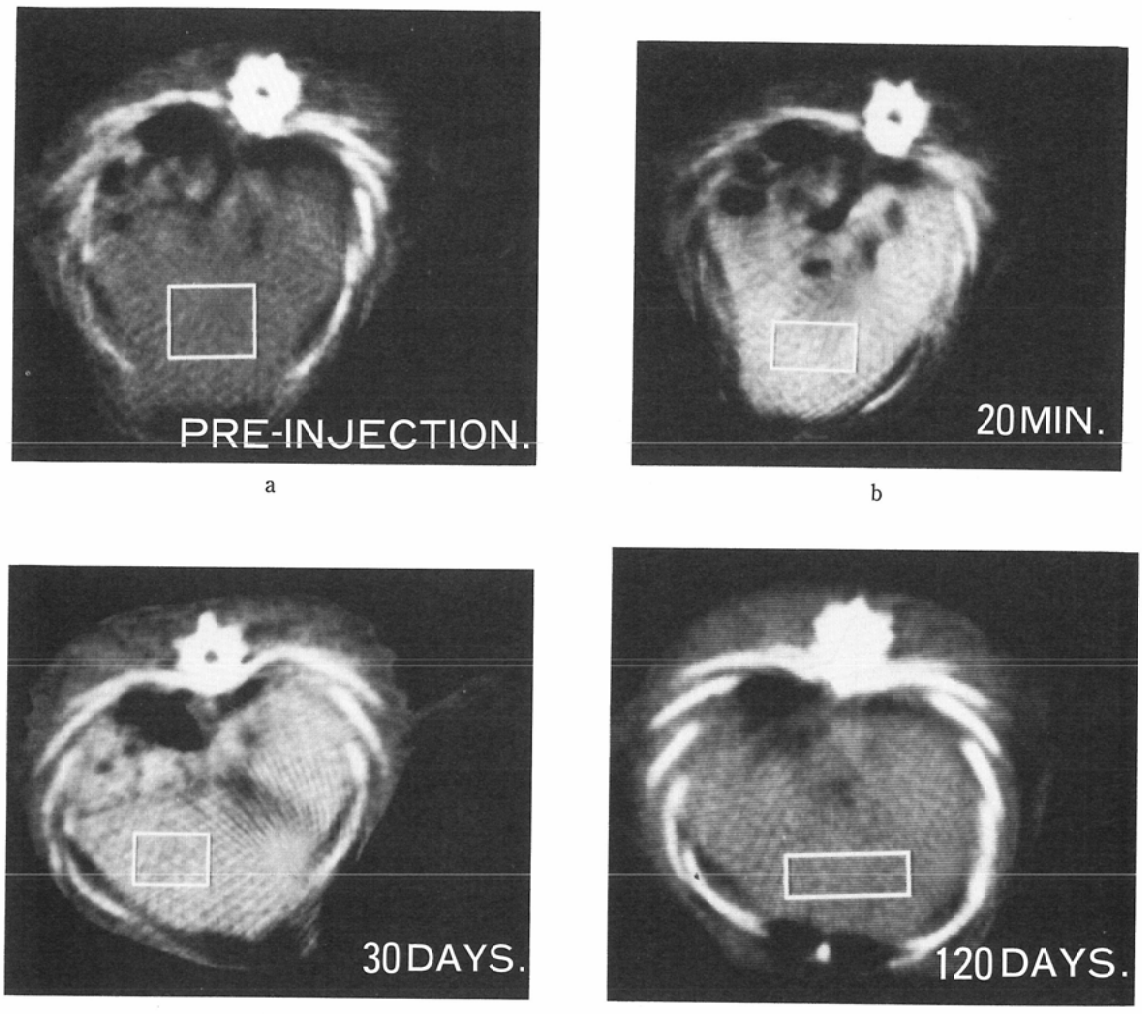
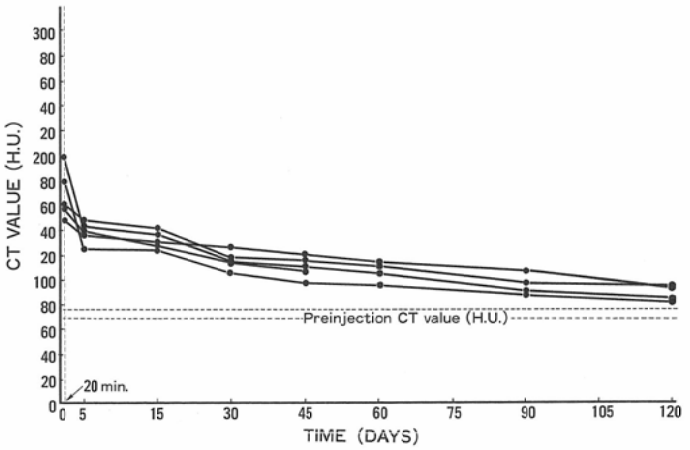


Fig. 2 CT scans of the rat liver before (a) and after (b, c, d) intravenous injection of 10% 0.3 μ B.S.P. suspension (2 ml/kg). The CT value in ROI is 74 H.U. in (a), 150 H.U. in (b), 114 H.U. in (c) and 83 H.U. in (d).

Kupffer cells containing B.S.P. between the periportal and perivenous regions. The cells were seen mostly in the periportal region and a few in the perivenous region (Fig. 4a, b). They decreased markedly in number with time in the periportal region, however, there was no significant change in the number in the perivenous region. They were less in the number in the perivenous region than in the periportal region throughout the observation period (Table 2). At one year, no B.S.P. could be found in any Kupffer cells in either the periportal or perivenous region.

4. Microscopic study on the quantity of B.S.P. within Kupffer cells

Immediately after the B.S.P. administration, every Kupffer cell seen in the periportal region was nearly completely filled with B.S.P. (Fig. 5). At 5 days after, however, when the hepatic CT values had slightly decreased, Kupffer cells were filled with various quantity of B.S.P., nearly completely (80 to 100%), moderately (40 to 80%) or slightly (10 to 40%). These cells were named "large", "medium" and "small" quantity of B.S.P., respectively (Fig. 6a, b, c). After it was confirmed by electron microscopy to be certain, these cells were counted by light microscopy (Fig. 7). Immediately after B.S.P. administration, every



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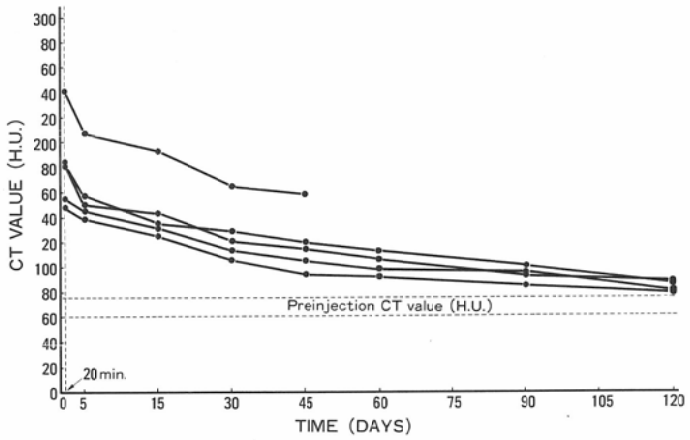

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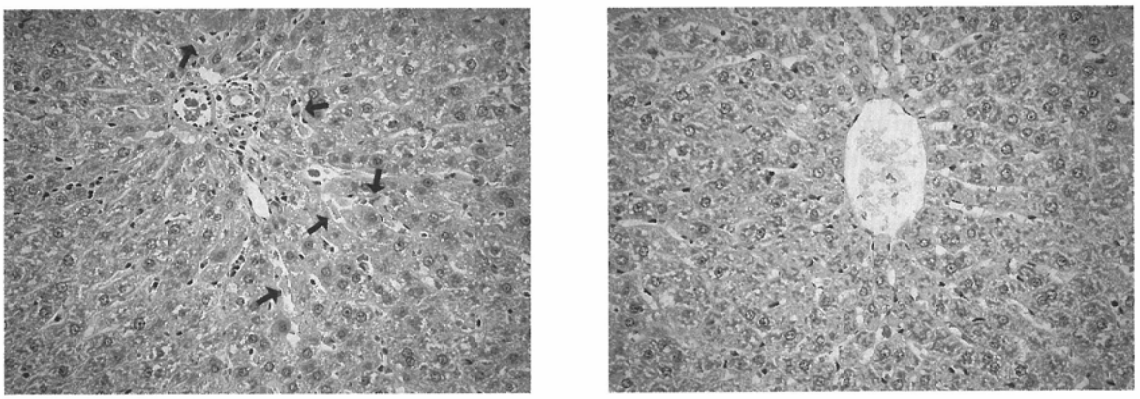
Fig. 3 Hepatic CT values after I.V. injection of 10% 0.3 μ (a) and 1.2 μ (b) B.S.P. suspensions.



a b

Fig. 4 Micrographs of the periportal ragion (a) and perivenous region (b) immediately after I.V. injection of 10% 1.2 μ B.S.P. suspension. Every Kupffer cell in the periportal region is filled with B.S.P. (arrow), while Kupffer cells in the perivenous region have no B.S.P. ×200.

Table 2 Number of Kupffer cells containing B.S.P. at various time after B.S.P. administration.

time after injection / number of Kupffer cells filled with B.S.P.	20 minutes		5 days		45 days		120 days	
	0.3μ	1.2μ	0.3μ	1.2μ	0.3μ	1.2μ	0.3μ	1.2μ
in periportal region	322±43	305±58	291±36	249±30	94±10	122±47	27±12	33±9
in perivenous region	15±2	15±3	17±4	18±8	14±8	17±7	8±3	6±5

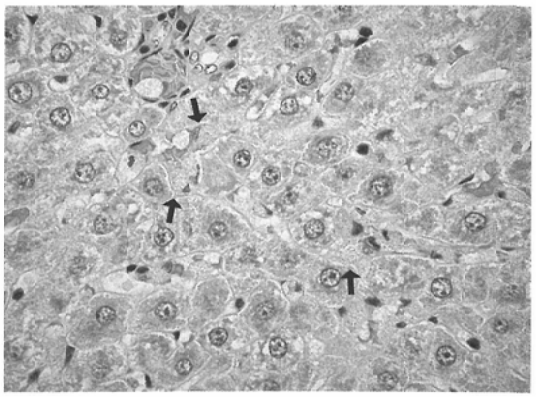
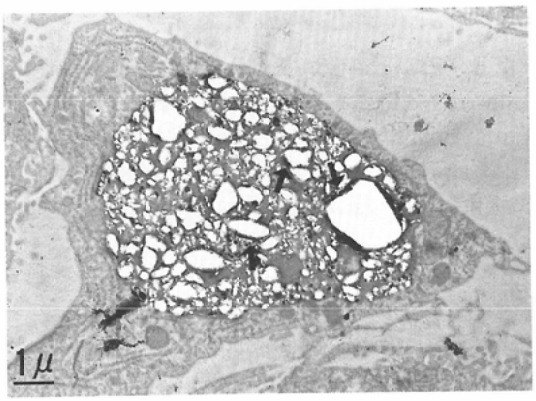


Fig. 5 Micrograph of the periportal region immediately after I.V. injection of 10% 1.2 μ B.S.P. suspension. Kupffer cells are nearly completely filled with B.S.P. in this region (arrow). ×400.



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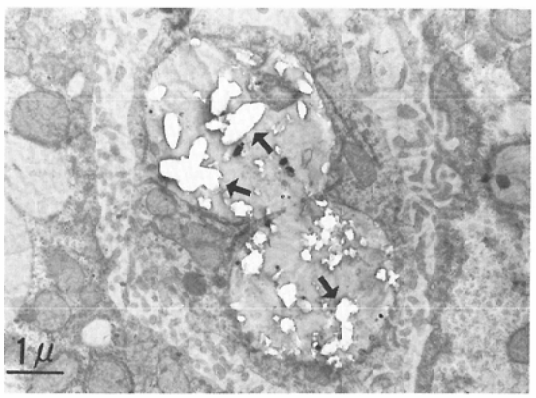

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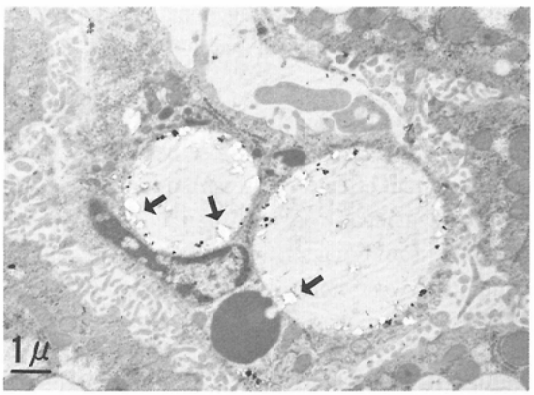

c

Fig. 6 Electron micrographs of Kupffer cells at 5 days after I.V. injection of 10% 0.3 μ B.S.P. suspension. Kupffer cells are filled with various quantity of B.S.P., nearly completely (a), moderately (b) and slightly (c). These are named "large", "medium" and "small" quantity of B.S.P., respectively. Many white round holes (arrow) within the Kupffer cell represent the cast-off spaces of B.S.P. made in the preparative process.

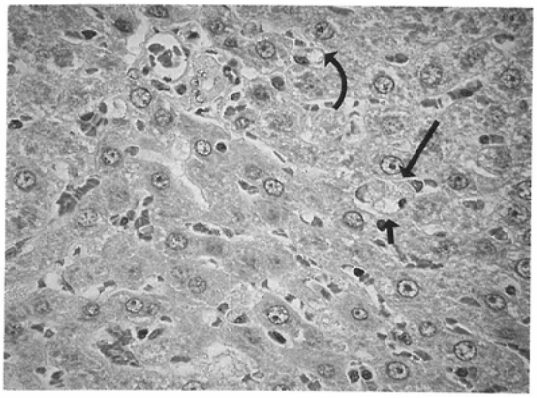

Fig. 7 Micrograph of the periportal region at 5 days after I.V. injection of 10% 1.2 μ B.S.P. suspension. Kupffer cells of "large" (long arrow), "medium" (short arrow) and "small" (curved arrow) quantity of B.S.P. are seen. ×400.

Table 3 Quantity of B.S.P. in Kupffer cells at various time after B.S.P. administration.

time after injection / quantity of B.S.P. in Kupffer cells	20 minutes		5 days		45 days		120 days	
	0.3μ	1.2μ	0.3μ	1.2μ	0.3μ	1.2μ	0.3μ	1.2μ
large	100%	100%	23±8%	33±5%	43±13%	33±11%	43±38%	45±20%
medium	0%	0%	25±2%	30±8%	30±11%	29± 8%	25±17%	20±13%
small	0%	0%	53±9%	38±3%	27± 6%	40±17%	32±22%	35±10%

Kupffer cell in the periportal region had "large" quantity of B.S.P. in the 0.3 μ B.S.P. group. However, the number of Kupffer cells of "large" quantity of 0.3 μ B.S.P. decreased to 23% at 5 days after and to 43% at 45 days and 120 days after, while Kupffer cells of "medium" and "small" quantity of B.S.P. were seen in 25% and 53% at 5 days after, 30% and 27% at 45 days after and 25% and 32% at 120 days after, respectively. The similar pattern was seen in the 1.2 μ B.S.P. group (Table 3). There were no morphological alternations such as fibrosis, granuloma or cell necrosis in the hepatic tissues.

Discussion

Studies on positive contrast media for hepatic CT have been carried out using various kinds of micro-particles[1)3)~9)11)~19)21)24)28)]. Since about 90% of RES is contained in the liver and spleen[4)8)29)], most of these agents are taken up by these organs, so that the liver is selectively enhanced. The enhancement effect of the liver by these agents was evaluated by conventional radiography before the invention of CT[10)20)22)23)25)~27)29)30)32)]. CT is appropriate for evaluating hepatic enhancement by these agents, since its improved densitometric capability permits marked reduction of the injection dose, compared with conventional radiography[14)16)17)].

These agents have a number of advantages over water-soluble contrast media in hepatic CT. First of all, they produce the sufficient effect at relatively low dose because of their selective uptake by Kupffer cells[5)7)]. In addition, once the enhancement effect has been obtained, it persists for a sufficiently long period of time throughout the entire area of the hepatic parenchyma[3)5)7)8)18)19)]. Secondly, they are selectively taken up by normal hepatic tissue but not by tumorous tissue, since most such lesions have no RES[33)]. Significant difference in contrast enhancement between normal hepatic and tumorous tissues facilitates detection of intrahepatic small lesions[1)4)5)7)8)13)14)16)~19)].

In 1957, Teplick et al.[10)] reported the enhancement effect of B.S.P. in the liver. The B.S.P. were 3 μ to 4 μ in diameter and suspended in distilled water. Conventional radiography demonstrated them to be taken up by the liver and spleen following an intravenous injection of B.S.P. to rabbits at a dose of 1 g/kg. However, two problems remained. First, the intravenous injection of B.S.P. caused pulmonary embolism due to aggregation of B.S.P.. Secondly, B.S.P. remained in the liver for more than one year after the administration.

Our experimental results gave rise to the following considerations.

1) Pulmonary embolism

The occurrence of small pulmonary capillary embolism following an intravenous injection of B.S.P. is probably related to particle size and clumping formation of individual paticles. In 1982, Laval-Jeantet et al.[3] found that pulmonary embolism tended to occur when the size of particles administered was 3 μ or more in diameter. The B.S.P. used in our study were 0.3 μ or 1.2 μ in diameter. In addition, it was shown by electron microscopy that individual particles were well separated from each other in a 5% glucose solution. Thus, there is little possibility of pulmonary embolism by our B.S.P.. However, the interaction of B.S.P. with serum protein may result in clumping of particles[23][31]. In 1979, Vermess et al.[17] indicated experimentally that injection dose may be another factor causing pulmonary embolism. They administered EOE-13 to rhesus monkeys at a dose of 30 times higher than its clinical dose and found a large amount of EOE-13 in the lungs of the dead monkeys. The dose (0.2 g/kg) of the B.S.P. suspensions administered intravenously to rats in our study was about one-fifth of the dose (1 g/kg) in the experiment of Teplick et al.[10] In our study, as a matter of fact, death of the animals occurred neither immediately after the intravenous injection of B.S.P. suspensions nor at any subsequent time for one year.

2) Retention of particles

Long-term retention of B.S.P. in Kupffer cells is the second problem pointed out by Teplick et al.[10] Prolonged retention of positive contrast media in the liver is disadvantageous for hepatic CT[4][8][13][18]. There are some reports on the release or elimination of agents from the liver after phagocytosis[9][11][12][20]. In our study, the maximum hepatic CT values decreased to one-half at 30 days after and subsequently decreased to one-fifth at 120 days after. Furthermore, the CT values at one year after were within the preinjection values and B.S.P. could be no longer detected microscopically in any Kupffer cells. These findings differ from the experimental results of Teplick et al.[10] The reason for this may be that the total dose of B.S.P. administered in our study was much less than in Teplick's experiment. The use of different animals may be another reason, since the turnover time of Kupffer cells differs according to the kind of animal. However, if the hepatic density would had been measured at one year after B.S.P. administration by Teplick et al., it should have been found considerably decreased.

3) Particle size

The size of particles taken up efficiently by the liver is about 1.0 μ in diameter[3][5]. In our study, the average hepatic CT value immediately after the administration of 1.2 μ particles was slightly but not significantly higher than that of 0.3 μ particles (Fig. 3a, b). Both 1.2 μ and 0.3 μ B.S.P. suspensions were administered at a same volume of 2 ml/kg and at a same concentration of 10% and thus the number of particles per volume of 1.2 μ B.S.P. suspension should be less than that of 0.3 μ B.S.P. suspension, since both suspensions have the same weight of B.S.P per volume. This is certainly a reason why hepatic CT values have no significant difference between two suspensions.

4) Distribution of Kupffer cells containing B.S.P.

In our microscopic study, there was an apparent difference in the distribution of Kupffer cells containing B.S.P. immediately after B.S.P. administration. Most of the cells were seen in the periportal region but only a few in the perivenous region. In 1982, Sleyster et al.[34] showed 40% of Kupffer cells to belong to the periportal region, while 20% to the perivenous region and the phagocytic activity of the cells to be higher in the periportal than other hepatic regions. Our results on the intrahepatic distribution of Kupffer cells containing B.S.P. can be explained by their results.

5) Clearance of B.S.P. and CT values

Every Kupffer cell in the periportal region was filled with "large" quantity of B.S.P. immediately after B.S.P. administration. Kupffer cells containing "medium" or "small" quantity of B.S.P. were come out with the decrease of Kupffer cells containing "large" quantity of B.S.P. at 5, 45 and 120 days after. Kupffer

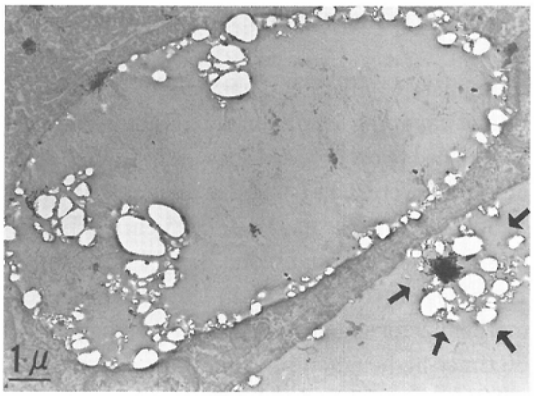

Fig. 8 Electron micrograph of Kupffer cell at 5 days after I.V. injection of 10% 0.3 μ B.S.P. suspension. Several white round holes (arrows) adjacent to the cytoplasmic membrane of Kupffer cell represent the cast-off spaces of B.S.P. in the extracellular space. B.S.P. are probably released from the Kupffer cell into the extracellular space.

cells containing B.S.P. were not significantly different in number between immediately after and at 5 days after, but they decreased markedly at 45 and 120 days after. Therefore, a decrease in hepatic CT values in the early period should result mainly from release of B.S.P. from the Kupffer cells. In addition, an electron microscopic study, which was performed in only one rat, showed several B.S.P. to adhere to the cytoplasmic membrane of Kupffer cells. It should suggest that B.S.P. had been released from Kupffer cells into the extracellular space (Fig. 8). Further decrease in hepatic CT values in the late period was probably due not only to this release but decrease in the number of the Kupffer cells as well. If the release of B.S.P. continues at the same rate after the 5th day, Kupffer cells containing "large" quantity of B.S.P. should decrease progressively in number, while Kupffer cells containing "medium" and "small" quantity of B.S.P. should increase in number. However, the percentages of the Kupffer cells containing "medium" and "small" quantity of B.S.P. remained almost unchanged between the 5th and 120th day (Table 3). Furthermore, the decreasing rate of CT values in the early period was higher than one in the late period. It can be presumed from these results that the decrease in hepatic CT values in the early period results from the release of B.S.P. from the Kupffer cells and the decrease in hepatic CT values in the late period results from the decrease in number of Kupffer cells containing B.S.P.. Renewal of Kupffer cells in the normal mouse liver can occur at a mean turnover time of 21 days, as described by Crofton et al.[35]

In 1969, Adlersberg et al.[36] reported a study on the redistribution and elimination of polystyrene-butadiene latex paritcles (PLP) after the intravenous injection into mice. PLP phagocytized by Kupffer cells migrated gradually from the liver to the lung in the postinjection period. Some particles left the pulmonary capillary bed to be phagocytized by proliferating interstitial alveolar cells. These cells moved up the bronchial tree and PLP were finally eliminated into the digestive tract. On the other hand, remaining particles in the pulmonary capillaries returned to the liver and spleen. We have performed no histological examination of the lung and thus cannot say whether B.S.P. are phagocytized by proliferating interstitial alveolar cells. However, the elimination process of PLP from the liver may be applicable to B.S.P. since both materials are inorganic. We consider that most B.S.P. are phagocytized by periportal Kupffer cells immediately after the administration and then these particles are released into the extracellular space. At the same time, Kupffer cells containing B.S.P. are slowly removed by cell renewal via bone marrow-derived

monocytes. B.S.P. in extracellular spaces move up to the lung through the venous flow. Some particles are then eliminated into the digestive tract through interstitial alveolar cells and residual particles return to the liver to be phagocytized again by Kupffer cells. As mentioned previously, the numbers of Kupffer cells containing "large", "meidum" and "small" quantity of B.S.P. remained unchanged between 5 and 120 days postinjection, although the CT values decreased progressively with time. This may be explained by the fact that B.S.P. are phagocytized again by Kupffer cells after the recirculation via the lung. The time for elimination of B.S.P. from the liver is much shorter than that of PLP. This may be due to the different kinds of materials, different experimental animals and different injection doses.

In our study, intravenous injections of B.S.P. suspensions caused significant increase in hepatic CT values in the early postinjection period and B.S.P. were eliminated slowly from the liver, finally disappearing without morphological alternation.

The present experimental results do not sufficiently warrant the use of B.S.P. as a positive contrast medium for hepatic CT, since no biodistribution or toxicity studies of B.S.P. have been performed. However, it should be useful for clinical use of micro-particles as a positive contrast medium for hepatic CT to study the behavior of micro-particles in the liver.

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